CERTIFIED COPY OF PRIORITY DOCUMENT

THE PATENTS ACT, 1970

It is hereby certified that annexed hereto is a true copy of Application, Provisional Specification & Complete Specification of the extract of Patent Application No. 156/MAS/2003, dated 28/02/2003 by Dr. Reddy's Laboratories Limited having its registered office at 7-1-27, Ameerpet, Hyderabad - 500 016, Andhra Pradesh, INDIA.

.....

.....In witness thereof

I have hereunto set my hand

Dated this the 08th day of September 2004

M.S. Venkataraman

(M.S. VENKATARAMAN)
Assistant Controller of Patents & Designs

PATENT OFFICE BRANCH
GOVERNMENT OF INDIA
Guna Complex, 6th Floor, Annex.II
No.443, Anna Salai, Teynampet, Chennai – 600 018

Received Rs. 500/- in Cash
Cheque/M.O./P.O./D.D/on 28.02.03
Vide C.B.R. No. 5364

FORM 1

THE PATENTS ACT, 1970
APPLICATION FOR GRANT OF A PATENT (Section 5(2), 7and Rule 33A)

We, Dr. Reddy's Laboratories Limited, an Indian company having its registered office at 7-1-27, Ameerpet, Hyderabad, Andhra Pradesh, INDIA, 500 016 hereby declare

(a) that we are in possession of an invention titled "**Novel crystalline form-Z of 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulfinyl]-1*H*-benzimidazole sodium and process for the preparation thereof (Rabeprazole sodium)** "

(b) that the complete specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

1. further declare that the inventors for the said invention are **Manne Satyanarayana Reddy, Sajja Eswaraiah, Bolugoddu Vijaya Bhaskar, Pingili Ramchandra Reddy, Ireddy Rajiv and Thirunava karasu. Ananda Babu** All citizens & residents of India belonging to **Dr. Reddy's Laboratories Limited, 7-1-27, Ameerpet, Hyderabad - 500 016, Andhra Pradesh.**

2. that we are the assignee of the true and first inventors

3. that our address for service in India is as follows;

Dr. M.Satyanarayana Reddy,
Vice President
Dr. Reddy's Laboratories Limited
7-1-27, Ameerpet
Hyderabad, A.P., 500 016

5. following declaration was given by inventors.

We, the true and first inventors for this invention declare that the applicant herein is our assignee.

Signed) _____

Manne Satyanarayana Reddy,
H.No: 8-3-167/D/16,
Kalyan Nagar
Near AG Colony
Erragadda
Hyderabad- 500 038

MAS 2003
156
24 FEB 2003
ORIGINAL

Signed)_____

Sajja Eswaraiah
LIG 110,
Dharma Reddy Colony,
K.P.H.B Colony
Kukatpally
Hyderabad - 500 072.

Signed)_____

Bolugoddu Vijaya Bhaskar
Flat. No. 209; S V Sumithra Apartments:
Sumithra Nagar; Kukat pally;
Hyderabad-500072
Andhrapradesh; India

Signed)_____

Pingili Ramchandra Reddy
H.No: 1-173/5; Snehapuri Colony;
Borabanda
Sanath Nagar;
Hyderabad-500018
Andhrapradesh; India

Signed)_____

Ireddy Rajiv
C/o Ramchander;
H.No : 5-5-7/27;
Devinagar Road No. 5; Kukatpally;
Hyderabad – 500 072
Andhrapradesh: India

Signed)_____

Thirunava karasu. Ananda Babu
C-71, Shanmugham Street;
Thirunagar; Madurai
Tamilnadu; India

6. that to the best of our knowledge, information and belief, the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application

7. following are the attachments with the application
   (a) complete specification (--11-- pages, in triplicate)
   (b) abstract of the invention (--1-- page, in triplicate)
   (c) drawings (--1-- pages, in triplicate)
   (d) fee Rs. 5000.00 (five thousand rupees only) in Cheque vide No "336961" dated February 6 th drawn on HDFC Bank, Lakdikapool ,Hyderabad- 500 004.

We request that a patent may be granted to us for the said invention

Dated this 23rd day of February, 2003.

(Signed) _____

Dr. M.Satyanarayana Reddy,
Vice President
Dr. Reddy's Laboratories Limited.

To,
The Controller of Patents
The Patents Office Branch, Chennai.

FORM-2

THE PATENTS ACT, 1970

PROVISIONAL SPECIFICATION

(SECTION 10)

Novel Crystalline form-Z of 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl] sulfinyl]-1*H*-benzimidazole sodium and process for the preparation thereof.

(Rabeprazole sodium)

Dr. Reddy's Laboratories Limited,

An Indian Company having its registered office at

7-1-27, Ameerpet,

Hyderabad-500 016, A.P., India.

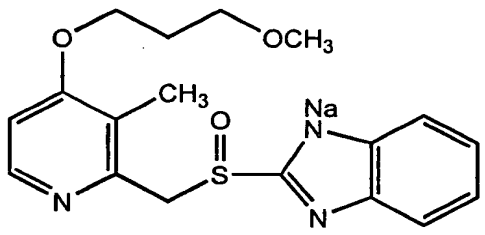
The following specification particularly describes the nature of this invention and the manner on which it is to be performed.

FIELD OF THE INVENTION

The present invention relates to the novel crystalline form of Rabeprazole sodium. The present invention also relates to methods of making novel crystalline form of Rabeprazole sodium.

BACK GROUND OF THE INVENTION

Achiphex ® (Rabeprazole sodium) is an inhibitor of the gastric proton pump. It causes dose-dependant inhibition of acid secretion and is useful as an antiulcer agent. The chemical designation of Rabeprazole sodium is 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl] sulfinyl]-1*H*-benzimidazole sodium. It may be represented by Formula (1):



Formula (1)

US Patent No. 5,045,552 incorporated herein by reference describes the synthesis of Rabeprazole and its sodium salt. Rabeprazole is prepared by oxidizing 2-[{4-(3-methoxypropoxy)-3-methylpyridine-2-yl} methylthio]-1H-benzimidazole with m-chloroperbenzoic acid to afford the Rabeprazole base, which is then converted to its sodium salt by aqueous sodium hydroxide solution.

Polymorphism is the occurrence of different crystalline forms of a single compound and it is a property of some compounds and complexes. Thus, polymorphs are distinct solids sharing the same molecular formula, yet each polymorph may have distinct physical

properties. Therefore a single compound may give rise to a variety of polymorphic forms where each form has different and distinct physical properties, such as different solubility profiles, different melting point temperatures and/or different X-Ray diffraction peaks. Since the solubility of each polymorph may vary, identifying the existence of pharmaceutical polymorphs is essential for providing pharmaceuticals with predictable solubility profiles. It is desirable to investigate all solid forms of a drug, including all polymorphic forms, and to determine the stability, dissolution and flow properties of each polymorphic form. Polymorphic forms of a compound can be distinguished in the laboratory by X-Ray diffraction spectroscopy and by other methods such as, infrared spectroscopy.

Crystal forms of Rabeprazole are mentioned in Japanese Patent 2001-39975 and designates them as crystal I and II, however does not identify crystal I by recognized methods of crystal structure identification such as X-Ray diffraction and also the above patent disclosed amorphous form of Rabeprazole Sodium.

The crystal II of Rabeprazole sodium however is discussed in detail and characterized by its X-Ray diffraction spectroscopy, Infrared spectroscopy and Differential Scanning Calorimetry.

The process for the preparation of crystal II as disclosed in the Japanese Patent specification comprises crystallization of amorphous Rabeprazole sodium or acetone complex of Rabeprazole sodium in one or more solvents selected from ethyl acetate, isopropyl acetate, isobutyl acetate, ethyl propionate, isobutyl propionate or ethyl butyrate.

The X-ray diffractogram for crystal II as in Japanese Patent 2001-39975 is as follows:

2 theta (°)	I/I_O (%)
19.52	100

17.20	41
26.60	28
20.92	18
18.04	17
24.76	13
21.20	12
14.22	10
17.60	10
25.00	10
29.40	10
28.76	9
27.56	7
27.76	7
12.54	5
13.20	5
24.38	5
28.50	5
34.04	5
13.80	4
22.64	4
24.16	4
30.00	4
31.62	3
12.82	3
34.92	2
25.92	2
11.84	2
8.88	1
9.64	1

Crystal forms of Rabeprazole Sodium are mentioned in Indian patent application 207 MAS 2002 and designate them as form X and form Y.

The form X and form-Y of Rabeprazole sodium however are discussed in detail and characterized by its X-Ray diffraction spectroscopy, Infrared spectroscopy and Differential Scanning Calorimetry.

The process for the preparation of form X as disclosed in the Indian patent application 207 MAS 2002 specification comprises

a) 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulfinyl]-1*H*-benzimidazole (prepared as per reference example 1) is dissolved in C_1-C_4 alkanol and an alkali hydroxide such as methanolic sodium hydroxide, ethanolic sodium hydroxide or isopropanolic sodium hydroxide or mixtures in the ratio between 1:1-1.34 preferably in the ratio of 1:1.34 thereof, preferably methanolic sodium hydroxide, accompanied by distilling the solvent from the reaction solution;

b) chlorinated lower hydrocarbon solvents such as dichloromethane, dichloroethane, trichloroethane, tetrachloroethane, dichloropropane, chloroform or carbon tetrachloride, preferably dichloromethane is added to the residual mass obtained in step a)

c) the residual solvent of alcohol is distilled off azeotropically under reduced pressure from the reaction solution of step b)

d) chlorinated lower hydrocarbon solvents such as dichloromethane, dichloroethane, trichloroethane, tetrachloroethane, dichloropropane, chloroform or carbon tetrachloride, preferably dichloromethane and an C_1-C_{10} alkane solvent as pentane, hexane, heptane, petether, octane, i-octane, nonane, decane or cyclic alkanes as cyclohexane, preferably petether; or mixtures thereof; such that the ratio of chlorinated lower hydrocarbon solvents to alkane solvent/ cyclic alkanes is in the range of 1:5-15 preferably 1:5-10 and more preferably 1:5 are added to the residue obtained in step c) and accompanied by stirring,

e) the desired form X is isolated by conventional methods.

The X-ray diffractogram for form X as in Indian patent application 207 MAS 2002 is as follows

form X

2 θ (°)	Intensity (cps)
5.13	1184
6.606	225
20.01	215
23.469	193
8.569	169
12.923	154
20.539	135
22.177	131
24.81	125
10.565	125
12.161	116
9.353	113
18.173	99.3
17.309	85.3
14.864	81.3
25.494	75.3
16.372	69.9
14.414	60.2
7.244	57.5
19.072	56.2

The Differential Scanning Calorimetry thermogram of crystalline form X exhibits a significant endo-exo pattern at 154.62^{O}C and 214.65^{O}C.

The melting range (capillary method) of crystalline form X is 140-150 ^{O}C.

The process for the preparation of form Y as disclosed in the Indian patent specification comprises

a) dissolving 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl] sulfinyl]-1*H*-benzimidazole (prepared as per reference example1) in C_1-C_4 alcoholic solution of alkali hydroxide such as methanolic sodium hydroxide, ethanolic sodium hydroxide or isopropanolic sodium hydroxide or mixtures in the ratio between 1:1-1.34 preferably in the ratio 1:1.34thereof, preferably methanolic

sodium hydroxide, accompanied by distilling the solvent from the reaction solution;

b) adding of chlorinated lower hydrocarbon solvents such as dichloromethane, dichloroethane, trichloroethane, tetrachloroethane, dichloropropane, chloroform or carbon tetrachloride, preferably dichloromethane to the residual mass obtained in step a

c) distilling the residual solvent of alcohol azeotropically under reduced pressure from the reaction solution of b

d) adding to the residue obtained in step c) either C_3-C_5 straight or branched chain alcohols such as n-propanol, isopropanol, n-butanol, 2-butanol or tert.butanol, preferably n-butanol and an ether solvents selected from diethyl ether, diisopropyl ether, diisobutyl ether, ditert.butyl ether or tert.butyl methyl ether, preferably tert.butyl methyl ether; or mixtures thereof; such that the ratio of alcohol solvent to ether solvent is in the range of 1:10-20 preferably 1: 15-20 and more preferably 1:16; accompanied by stirring,

e) Isolation of desired Polymorph form Y by conventional methods.

The X-ray diffractogram for form Y as in Indian patent application 207 MAS 2002 is as follows

Form Y

2 θ (°)	Intensity (cps)
5.61	1635
19.442	546
18.816	329
7.725	285
7.207	242
9.649	235

10.352	219
16.899	186
24.943	162
16.418	104
14.546	103
11.231	77.0

The Differential Scanning Calorimetry thermogram of crystalline form Y exhibits a significant endo-exo pattern respectively at 182.61°C and 215.57°C.

The melting range (capillary method) of crystalline form Y is 160-170 °C.

It is an object of the present invention to provide novel crystalline form of Rabeprazole sodium designated as form Z for convenience.

Another object of the present invention is to provide a process for the preparation of novel crystalline form Z of Rabeprazole sodium.

form Z of Rabeprazole sodium show better chemical stability such as thermo stability and light stability.

SUMMARY OF THE INVENTION

Accordingly, the present invention is directed to novel crystalline form of Rabeprazole sodium. This crystalline form of Rabeprazole sodium is designated as form Z for convenience.

The present invention further provides a process for the preparation of novel crystalline form Z of Rabeprazole sodium, which is a commercially viable process and well suited for industrial scale up.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides novel crystalline form Z of Rabeprazole sodium. This solid-state form includes hydrated crystalline forms. The crystalline form Z of the present invention may be characterized by their X Ray powder diffraction. Thus the X-Ray diffraction pattern of form Z of Rabeprazole sodium was measured on a Bruker Axs, D8 Advance Powder X-ray Diffractometer with Cu K alpha-1 Radiation source.

Crystalline form Z has X-ray powder diffraction pattern essentially as shown in the Table 1. The X-ray powder diffraction pattern is expressed in terms of the 2θ, and relative intensities (cps).

Table 1:

2 θ (°)	Intensity (cps)	Intensity I/I_o
4.694	5710	100
9.070	147	2.6
9.417	42.1	0.7
11.254	200	3.5
14.712	181	3.2
16.241	141	2.5
17.264	94	1.6
18.522	87.9	1.5
18.522	297	5.2
19.320	829	14.5
19.626	368	6.4
19.920	84.6	1.5
20.802	122	2.1
21.477	40.20	0.7
23.073	110	1.9
24.814	143	2.5
25.702	138	2.4
27.470	179	3.1
30.009	56.5	1
30.653	39	0.7
33.365	49	0.9
36.950	61	1.1

The present invention also provides form Z of Rabeprazole sodium that is characterized by its X Ray powder diffraction.

The present invention also provides the Differential Scanning Calorimetry thermogram of form Z of Rabeprazole sodium The Differential Scanning Calorimetry thermogram exhibits a significant endo-exo pattern respectively at 106.5^{O}C and 228.8^{O}C..

The present invention also provides melting range (capillary method) of crystalline form Z at 224-230^{O}C.

Accordingly the present invention also provides a process for the preparation of form Z of Rabeprazole sodium, which comprises;

a) adding amorphous form or form-X or form Y of Rabeprazole Sodium having the chemical name sodium salt of 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl] sulfinyl]-1*H*-benzimidazole [prepared as per reference example 2 (amorphous) and Reference example 3 (form X) and reference example 4 (form Y)] to aromatic hydrocarbon solvents such as toluene and xylenes preferably toluene in the ratio between 1:3 to 1:20 preferably in the ratio of 1:4.

b) heating or reflux reaction mixture for 1-10 hrs azeotropically. Preferably 2-6 hrs.

c) cooling the reaction mixture to 0-40°C preferably to 25-35°C.

d) isolation of desired form Z by conventional methods.

The crystalline form Z of Rabeprazole sodium of the present invention is having high melting transition temperature in which residual solvents are within permissible limits and is very well suited for pharmaceutical application

Dated 23rd day of February 2003

Signed _____
Dr. Manne Satyanarayana Reddy,
Vice-president (R&D)
Dr.Reddy's Laboratories Limited.

FORM-2

THE PATENTS ACT, 1970

156/MAS/03
28-2-03

COMPLETE SPECIFICATION

(SECTION 10)

Complete After Provisional
Left 25 FEB 2004

Novel Crystalline form-Z of 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl] sulfinyl]-1*H*-benzimidazole sodium (Rabeprazole sodium) and process for the preparation thereof.

Dr. Reddy's Laboratories Limited,

An Indian Company having its registered office at

7-1-27, Ameerpet,

Hyderabad-500 016, A.P., India.

ORIGINAL
25 FEB 2004

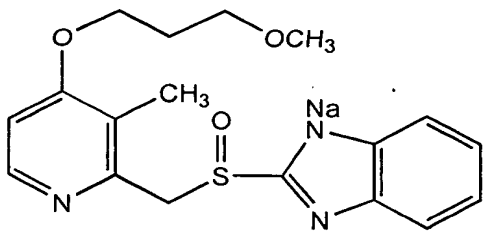
The following specification particularly describes the nature of this invention and the manner on which it is to be performed.

FIELD OF THE INVENTION

The present invention relates to the novel crystalline form of Rabeprazole sodium. The present invention also relates to methods of making novel crystalline form of Rabeprazole sodium.

BACK GROUND OF THE INVENTION

Achiphex ® (Rabeprazole sodium) is an inhibitor of the gastric proton pump. It causes dose-dependant inhibition of acid secretion and is useful as an antiulcer agent. The chemical designation of Rabeprazole sodium is 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl] sulfinyl]-1*H*-benzimidazole sodium. It may be represented by Formula (1):



Formula (1)

US Patent No. 5,045,552 incorporated herein by reference describes the synthesis of Rabeprazole and its sodium salt. Rabeprazole is prepared by oxidizing 2-[{4-(3-methoxypropoxy)-3-methylpyridine-2-yl} methylthio]-1H-benzimidazole with m-chloroperbenzoic acid to afford the Rabeprazole base, which is then converted to its sodium salt by aqueous sodium hydroxide solution.

Polymorphism is the occurrence of different crystalline forms of a single compound and it is a property of some compounds and complexes. Thus, polymorphs are distinct solids sharing the same molecular formula, yet each polymorph may have distinct physical properties. Therefore a single compound may give rise to a variety of polymorphic forms where each form has different and distinct physical properties, such as different solubility profiles, different melting point temperatures and/or different X-Ray diffraction peaks. Since the solubility of each polymorph may vary, identifying the existence of pharmaceutical polymorphs is essential for providing pharmaceuticals with predictable solubility profiles. It is desirable to investigate all solid forms of a drug, including all polymorphic forms, and to determine the stability, dissolution and flow properties of each polymorphic form. Polymorphic forms of a compound can be distinguished in the laboratory by X-Ray diffraction spectroscopy and by other methods such as, infrared spectrometry.

Crystal forms of Rabeprazole are mentioned in Japanese Patent 2001-39975 and designates them as crystal I and II, however does not identify crystal I by recognized methods of crystal structure identification such as X-Ray diffraction and also the above patent disclosed amorphous form of Rabeprazole Sodium.

The crystal II of Rabeprazole sodium however is discussed in detail and characterized by its X-Ray diffraction spectroscopy, Infrared spectrometry and Differential Scanning Calorimetry.

The process for the preparation of crystal II as disclosed in the Japanese Patent specification comprises crystallization of amorphous Rabeprazole sodium or acetone complex of Rabeprazole sodium in one or more solvents selected from ethyl acetate, isopropyl acetate, isobutyl acetate, ethyl propionate, isobutyl propionate or ethyl butyrate.

The X-ray diffractogram for crystal II as in Japanese Patent 2001-39975 is as follows:

2 theta (°)	**I/I_O (%)**
19.52	100
17.20	41
26.60	28
20.92	18
18.04	17
24.76	13
21.20	12
14.22	10
17.60	10
25.00	10
29.40	10
28.76	9
27.56	7
27.76	7
12.54	5
13.20	5
24.38	5
28.50	5
34.04	5
13.80	4
22.64	4
24.16	4
30.00	4
31.62	3
12.82	3
34.92	2
25.92	2
11.84	2
8.88	1
9.64	1

Crystal forms of Rabeprazole Sodium are mentioned in Indian patent application 207 MAS 2002 and designate them as form X and form Y.

The form X and form-Y of Rabeprazole sodium however are discussed in detail and characterized by its X-Ray diffraction spectroscopy, Infrared spectrometry and Differential Scanning Calorimetry.

The process for the preparation of form X as disclosed in the Indian patent application 207 MAS 2002 specification comprises

a) 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulfinyl]-1*H* benzimidazole (prepared as per reference example 1) is dissolved in C_1-C_4 alkoanol and an alkali hydroxide such as methanolic sodium hydroxide, ethanolic sodium hydroxide or isopropanolic sodium hydroxide or mixtures in the ratio between 1:1-1.34 preferably in the ratio of 1:1.34 thereof, preferably methanolic sodium hydroxide, accompanied by distilling the solvent from the reaction solution;

b) chlorinated lower hydrocarbon solvents such as dichloromethane, dichloroethane, trichloroethane, tetrachloroethane, dichloropropane, chloroform or carbon tetrachloride, preferably dichloromethane is added to the residual mass obtained in step a)

c) the residual solvent of alcohol is distilled off azeotropically under reduced pressure from the reaction solution of step b)

d) chlorinated lower hydrocarbon solvents such as dichloromethane, dichloroethane, trichloroethane, tetrachloroethane, dichloropropane, chloroform or carbon tetrachloride, preferably dichloromethane and an C_1-C_{10} alkane solvent as

pentane, hexane, heptane, petether, octane, i-octane, nonane, decane or cyclic alkanes as cyclohexane, preferably petether; or mixtures thereof; such that the ratio of chlorinated lower hydrocarbon solvents to alkane solvent/ cyclic alkanes is in the range of 1:5-15 preferably 1:5-10 and more preferably 1:5 are added to the residue obtained in step c) and accompanied by stirring,

e) the desired form X is isolated by conventional methods.

The X-ray diffractogram for form X as in Indian patent application 207 MAS 2002 is as follows

form X

2 θ (°)	**Intensity (cps)**
5.13	1184
6.606	225
20.01	215
23.469	193
8.569	169
12.923	154
20.539	135
22.177	131
24.81	125
10.565	125
12.161	116
9.353	113
18.173	99.3
17.309	85.3
14.864	81.3
25.494	75.3
16.372	69.9
14.414	60.2
7.244	57.5
19.072	56.2

The Differential Scanning Calorimetry thermogram of crystalline form X exhibits a significant endo-exo pattern at 154.62^{O}C and 214.65^{O}C.

The melting range (capillary method) of crystalline form X is 140-150 ^{O}C.

The process for the preparation of form Y as disclosed in the Indian patent specification comprises

a) dissolving 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl] sulfinyl]-1*H*-benzimidazole (prepared as per reference example1) in C_1-C_4 alcoholic solution of alkali hydroxide such as methanolic sodium hydroxide, ethanolic sodium hydroxide or isopropanolic sodium hydroxide or mixtures in the ratio between 1:1-1.34 preferably in the ratio 1:1.34thereof, preferably methanolic sodium hydroxide, accompanied by distilling the solvent from the reaction solution;

b) adding of chlorinated lower hydrocarbon solvents such as dichloromethane, dichloroethane, trichloroethane, tetrachloroethane, dichloropropane, chloroform or carbon tetrachloride, preferably dichloromethane to the residual mass obtained in step a

c) distilling the residual solvent of alcohol azeotropically under reduced pressure from the reaction solution of b

d) adding to the residue obtained in step c) either C_3-C_5 straight or branched chain alcohols such as n-propanol, isopropanol, n-butanol, 2-butanol or tert.butanol, preferably n-butanol and an ether solvents selected from diethyl ether, diisopropyl ether, diisobutyl ether, ditert.butyl ether or tert.butyl methyl ether, preferably tert.butyl methyl ether; or mixtures thereof; such that the

ratio of alcohol solvent to ether solvent is in the range of 1:10-20 preferably 1: 15-20 and more preferably 1:16; accompanied by stirring,.

e) Isolation of desired Polymorph form Y by conventional methods.

The X-ray diffractogram for form Y as in Indian patent application 207 MAS 2002 is as follows

form Y

2 θ (°)	Intensity (cps)
5.61	1635
19.442	546
18.816	329
7.725	285
7.207	242
9.649	235
10.352	219
16.899	186
24.943	162
16.418	104
14.546	103
11.231	77.0

The Differential Scanning Calorimetry thermogram of crystalline form Y exhibits a significant endo-exo pattern respectively at 182.61°C and 215.57°C.

The melting range (capillary method) of crystalline form Y is 160-170 °C.

It is an object of the present invention to provide novel crystalline form of Rabeprazole sodium designated as form Z for convenience.

Another object of the present invention is to provide a process for the preparation of novel crystalline form Z of Rabeprazole sodium.

form Z of Rabeprazole sodium show better chemical stability such as thermo stability and light stability.

SUMMARY OF THE INVENTION

Accordingly, the present invention is directed to novel crystalline form of Rabeprazole sodium. This crystalline form of Rabeprazole sodium is designated as form Z for convenience.

The present invention further provides a process for the preparation of novel crystalline form Z of Rabeprazole sodium, which is a commercially viable process and well suited for industrial scale up.

BRIEF DESCRIPTION OF ACCOMPANYING DRAWINGS

Fig. 1 is characteristic X ray powder diffractogram of form Z of Rabeprazole sodium.

Fig. 2 is Differential Scanning Calorimetry thermogram of form Z of Rabeprazole sodium.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides novel crystalline form Z of Rabeprazole sodium. This solid-state form includes non-solvated and hydrated crystalline forms. The crystalline form Z of the present invention may be characterized by their X Ray powder diffraction. Thus the X-Ray diffraction pattern of form Z of Rabeprazole sodium was measured on a

Bruker Axs, D8 Advance Powder X-ray Diffractometer with Cu K alpha-1 Radiation source.

Crystalline form Z has X-ray powder diffraction pattern essentially as shown in the Table 1. The X-ray powder diffraction pattern is expressed in terms of the 2θ, and relative intensities (cps).

Table 1:

2 θ (°)	**Intensity (cps)**	**Intensity I/I_o**
4.694	5710	100
9.070	147	2.6
9.417	42.1	0.7
11.254	200	3.5
14.712	181	3.2
16.241	141	2.5
17.264	94	1.6
18.522	87.9	1.5
18.522	297	5.2
19.320	829	14.5
19.626	368	6.4
19.920	84.6	1.5
20.802	122	2.1
21.477	40.20	0.7
23.073	110	1.9
24.814	143	2.5
25.702	138	2.4
27.470	179	3.1
30.009	56.5	1
30.653	39	0.7
33.365	49	0.9
36.950	61	1.1

The present invention also provides form Z of Rabeprazole sodium that is characterized by its X Ray powder diffraction substantially as depicted in Figure 1.

The present invention also provides the Differential Scanning Calorimetry thermogram of form Z of Rabeprazole sodium The Differential Scanning Calorimetry thermogram exhibits a significant endo-exo pattern respectively at 106.5^{O}C and 228.8^{O}C..

The present invention also provides Differential Scanning Calorimetry thermogram of form Z of Rabeprazole sodium substantially as depicted in Figure 2.

The present invention also provides melting range (capillary method) of crystalline form Z at 224-230^{O}C.

Accordingly the present invention also provides a process for the preparation of form Z of Rabeprazole sodium, which comprises;

a) adding amorphous form or form-X or form Y of Rabeprazole Sodium having the chemical name sodium salt of 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl] sulfinyl]-1*H*-benzimidazole [prepared as per reference example 2 (amorphous) and Reference example 3 (form X) and reference example 4 (form Y)] to aromatic hydrocarbon solvents such as toluene and xylenes preferably toluene in the ratio between 1:3 to 1:20 preferably in the ratio of 1:4.

b) heating or reflux reaction mixture for 1-10 hrs azeotropically. Preferably 2-6 hrs.

c) cooling the reaction mixture to 0-40°C preferably to 25-35°C.

d) isolation of desired form Z by conventional methods.

The crystalline form Z of Rabeprazole sodium of the present invention is having high melting transition temperature in which residual solvents are within permissible limits and is very well suited for formulation.

DETAILED DESCRIPTION OF THE ACCOMPANYING DRAWING

Fig-1 is characteristic X-ray powder diffraction pattern of form Z of 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl] sulfinyl]-1*H*-benzimidazole sodium (Rabeprazole sodium).

Vertical axis: Intensity (CPS); Horizontal axis: 2θ (degrees). The significant 2θ values (in degrees) obtained are

4.694,9.070,9.417,11.254,14.712,16.241,17.264,18.522,18.522,19.320,19.626,19.920,20.802.21.477,23.073,24.814.25.702,27.470,30.009,30.653,33.365and36.950.

Fig-2 is Differential Scanning Calorimetry thermogram of form Z of 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl] sulfinyl]-1*H*-benzimidazole sodium (Rabeprazole sodium). The Differential Scanning Calorimetry thermogram exhibits a significant endo-exo pattern respectively at 105-110°C and 226-234°C.

The present invention is illustrated by the following examples, which are not intended to limit the effective scope of the claims.

Reference Example 1:

Preparation of 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl] sulfinyl]-1*H*-benzimidazole (Rabeprazole)

2-[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl thio]-1*H*-benzimidazole (Prepared as per example 90 of the Patent No. 5,045,552)(100grams, 0.29 moles) is added to a mixture of chloroform (9500 ml) and dimethylsulphoxide (200ml) and the reaction mixture is cooled to-10 to-15 degree c. 3-chloroperbenzoic acid (60grams,0.24 moles) is dissolved in chloroform (500ml), and added to the above solution at –10 to-15 for about 1- 2 hours and the reaction mixture is maintained at the temperature for 30 minutes. Thereafter 12.8%w/v aqueous sodium hydroxide solution (500ml) is added to the reaction mixture. The pH of the reaction mixture is adjusted to 9.5 to 10.0 with acetic acid. From the biphasic system thus obtained, the organic layer is separated and then extracted with 1.6%w/v aqueous sodium hydroxide solution (500ml). Further the sodium hydroxide extract is diluted with a mixture of chloroform (140ml) and methanol (100ml). Then the pH of the mass is again adjusted to 9.5 to 10.0 with acetic acid and the organic layer separated again. To the separated organic layer is now added tert. Butyl methyl ether (440ml).The reaction mixture is stirred for about 1-2 hours at a temperature of 0-5°C and subjected to filtration. The residue is dissolved in a mixture of 1:10% w/v aqueous sodium hydroxide solution (100ml) and methanol (65ml). The pH is adjusted to 9.0 to 9.5 with acetic acid at 10-15C and further stirred for 2 hours followed by

filteration . The wet material is then dissolved in dichloromethane (130ml) and the water layer separated where after solution is added to tert.butyl methy ether (260ml), stirred at a temperature of 0-5C for 1-2 hours. The 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl] sulfinyl]-1*H*-benzimidazole thus obtained is filtered and dried.

Reference Example 2:

Preparation of amorphous form of 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl] sulfinyl]-1*H*-benzimidazole sodium (Rabeprazole sodium):

2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl] sulfinyl]-1*H*-benzimidazole (obtained as per reference example) (50.0 grams, 0.139 moles) is dissolved in a mixture of sodium hydroxide (7.5 grams, 0.187 moles) and methanol (100.0 ml) and stirred at ambient temperature 25-35°C. The reaction solution is filtered through hi-flow and washed with methanol (50.0 ml). Then the solvent of the filtrate is distilled off under reduced pressure. The reaction mass is cooled to ambient temperature followed by addition of petroleum ether (400.0 ml) is then added to the residual mass, which is then stirred at 25-30°C for about 1-2 hours. The precipitated solid is filtered and washed with petroleum ether (100.0 ml) and dried at 50-60°C for 12 hours to afford the desired amorphous form of Rabeprazole sodium (Weight: 50.4 grams, 94.9%)

Reference Example 3:

Preparation of Crystalline form X of 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl] sulfinyl]-1*H*-benzimidazole sodium (Rabeprazole sodium):

2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl] sulfinyl]-1*H*-benzimidazole (obtained by reference example 1) (50.0 grams, 0.139 moles) is dissolved in a mixture of

sodium hydroxide (7.5 grams, 0.187 moles) and methanol (100.0 ml) and stirred at ambient temperature 25-35°C. The reaction solution is filtered through hi-flow and washed with methanol (50.0 ml). Then the solvent of the filtrate is distilled off under reduced pressure. The reaction mass is cooled to ambient temperature followed by addition of dichloromethane (100.0 ml) accompanied by distillation to remove traces of methanol. Dichloromethane (50.0 ml) and petroleum ether (100.0 ml) is then added to the residual mass, which is then stirred at 25-30°C for about 6-8 hours. The solid that obtained is further diluted with petroleum ether (150 ml) and stirred at 25-30°C for 1-2 hours. The precipitated solid is filtered and washed with petroleum ether (100.0 ml) and dried at 50-60°C for 12 hours to afford the desired form X of Rabeprazole sodium (Weight: 50.4 grams, 94.9%)

Reference example 4:

Preparation of Crystalline form-Y of 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl] sulfinyl]-1*H*-benzimidazole sodium (Rabeprazole sodium):

2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl] sulfinyl]-1*H*-benzimidazole (obtained as per reference example 1) (750.0 grams, 2.089 moles) is dissolved in a mixture of sodium hydroxide (112.5 grams, 2.8125 moles) and methanol (1500.0 ml) and stirred at ambient temperature 25-35°C. The reaction solution is filtered through hi-flow and washed with methanol (750.0 ml). Then the solvent of the filtrate is distilled off completely under reduced pressure. The reaction mass is cooled to ambient temperature followed by addition of dichloromethane (1500.0 ml) accompanied by distillation to remove traces of methanol. The reaction mass is cooled to ambient temperature and n-butanol (375.0 ml) and tertiary butyl methyl ether (6.0 lit) is added to the residual mass

which is stirred at 25-30^{O}C for 6-8 hours. The reaction mixture is further cooled to 5-15^{O}C and then stirred for another 3-5 hours. The solid thus obtained is filtered and washed with tertiary butyl methyl ether (1500.0 ml) and dried at 50-60^{O}C for 7 hours to afford the desired crystalline Form Y of Rabeprazole sodium (Weight: 725.0 grams, 91.1%)

Example 1:

Preparation of Crystalline form Z of 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl] sulfinyl]-1*H*-benzimidazole sodium (Rabeprazole sodium) from 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl] sulfinyl]-1*H* benzimi dazole (Rabeprazole):

2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl] sulfinyl]-1*H*-benzimidazole (obtained by reference example 1) (50.0 grams, 0.139 moles) is dissolved in a mixture of sodium hydroxide (7.5 grams, 0.187 moles) and methanol (100.0 ml) then stirred at ambient temperature 25-35^{o}C for about one hour. The reaction solution is filtered through hi-flow and washed with methanol (50.0 ml). Then the solvent of the filtrate is distilled off under reduced pressure. The reaction mass is cooled to ambient temperature followed by addition of Toulene (200.0 ml) to the residual mass, which is then refluxed for about 2-6 hours. The precipitated solid is filtered, washed with Toluene (100.0 ml) and dried at 90-100^{O}C for 12 hours to afford the desired form Z of Rabeprazole sodium (Weight: 50.4 grams, 94.9%)

Example 2: Preparation of Crystalline form Z of 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl] sulfinyl]-1*H*-benzimidazole sodium (Rabeprazole sodium):

Amorphous form or form-X or form Y of Rabeprazole Sodium having the chemical name Sodium salt of 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl] sulfinyl]-1*H*-benzimidazole [prepared as per reference example 2 (amorphous) and Reference example 3 (Form X) and reference example 4 (form Y)] (50.0 grams, 0.131 moles) is charged in to toluene (200.0 ml) and the mixture is heated to reflux temperature, then it is maintained at reflux temperature for 8-10 hrs. The reaction mixture is then cooled to 25-35°C. The precipitated solid is filtered off, washed with toluene (100.0 ml) and dried at 90-100°C for 6-8 hours to afford the desired form Z of Rabeprazole sodium (Weight: 45 grams, 90%)

The X-ray Diffraction Pattern, Differential Scanning Calorimetry thermogram of form Z of Rabeprazole sodium obtained in above example is in accordance to Figure 1 and 2 respectively.

We claim:

1. A crystalline form Z of 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl] sulfinyl]-1*H*-benzimidazole sodium (Rabeprazole sodium)
2. The crystalline form Z of Rabeprazole sodium of claim 1 having X-ray powder diffraction pattern with peaks at about 4.694,9.070,9.417,11.254,14.712,16.241,17.264,18.522,18.522,19.320,19.626,19.920,20.802.21.477,23.073,24.814.25.702,27.470,30.009,30.653,33.365,and 36.950 degrees 2 theta.

3. The crystalline form Z of Rabeprazole sodium of claim 1 having an X-ray powder diffraction pattern substantially as depicted in Figure 1.

4. The crystalline form Z of Rabeprazole sodium of claim 1 having a differential scanning calorimetery thermogram which exhibits a significant endo-exo pattern respectively at 105-110^{O}C and 226-234^{O}C.

5. The crystalline form Z of Rabeprazole sodium of claim 1 having characteristic Differential Scanning Calorimeter thermogram as depicted in Figure 2.

6. The crystalline form Z of Rabeprazole sodium of claim 1 having melting range of 220-230 ^{O}C.

7. A process for preparing form Z of Rabeprazole sodium from Rabeprazole.

8. A process for preparing form Z of Rabeprazole sodium from amorphous Rabeprazole sodium.

9. A process for preparing form Z of Rabeprazole sodium from form X of Rabeprazole Sodium.

10. A process for preparing form Z of Rabeprazole sodium from form Y of Rabeprazole Sodium.

11. A process for preparing form Z of 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl] sulfinyl]-1*H*-benzimidazole sodium (form Z of Rabeprazole sodium) using aromatic hydrocarbon solvents such as toluene and xylenes.

12. Novel crystalline form-Z of 2-[[[4-3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulfinyl]-1H-benzimidazole sodium(Rabeprazole sodium) and process for the preparation thereof, which is herein described and exemplified.

Dated this 16th day of February, 2004.

(Signed) S. Venkataraman
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